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Allan Svendsen

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EXAMINER

HA, JULIE

ART UNIT

PAPER NUMBER

1654

NOTIFICATION DATE

DELIVERY MODE

10/23/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents-US-NY@novozymes.com

Office Action Summary	Application No. 10/562,021	Applicant(s) SVENDSEN ET AL.	
	Examiner JULIE HA	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 1-5,7,11,13,14 and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6,8-10,12 and 15-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/22/05, 5/7/09, 8/13/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Election/Restriction filed on July 17, 2009 is acknowledged. New claims 15-18 have been added. Claims 1-18 are pending in this application.

Restriction

1. Applicant's election with traverse of Group 2 and the election of species of the polypeptide having an insertion of DPAGF between amino acids corresponding to amino acids 196 and 197 and substitution V16A of SEQ ID NO: 6 in the reply filed on July 17, 2009 is acknowledged. The traversal is on the ground(s) that there would not be a search burden to examine all the claims together. Furthermore, Applicant argues that "no objection to unity of invention was raised at any point of the PCT phase." This is not found persuasive because restriction in a national stage entry is based on unity of invention, not search burden. "Examiners are reminded that unity of invention (not restriction practice pursuant to 37 CFR 1.141 -1.146) is applicable in international applications (both Chapter I and II) and in national stage applications submitted under 35 U.S.C. 371." See MPEP 1893.03(d). Further, each amino acid sequence requires searching on 5-10 databases and each nucleic acid sequence requires searching on a different 5-10 database, thus had search burden been an applicable argument, there would have been a burden for the examiner to search all of the sequences on all of the relevant databases. The lack of unity was established in the previous office action. The special technical feature of the polypeptide of claim 6 (invention 2) is taught by WO 99/43793 A. WO 99/43793 teaches a polypeptide having at least 70% identity with

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parent CGTase, and has at least one mutation at the regions selected from group comprising the regions corresponding to amino acids 78-85, 136-139, 173-180, 188-195 and 259-268. The positions 78-85 and 136-139, 173-180, 188-195 and 259-268 overlap the positions 85-95, 139, 174, 191 and 260-269 of instant claim 6. Therefore, the lack of unity has been established.

2. The requirement is still deemed proper and is therefore made FINAL. Claims 1-5, 7, 13-14 have been withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 11 and 18 are further withdrawn from consideration, as being drawn to nonelected species. A search was conducted on the elected species, and a prior art having a polypeptide having an insertion DPAGF between amino acids corresponding to amino acids 196 and 197. A search was conducted on the species having a polypeptide having an insertion DPAGF and V16A substitution was free of prior art. A search was extended to the other species, and prior art was found. **Claims 6, 8-10, 12 and 15-17 are examined on the merits in this office action.**

TRADEMARK

3. The use of the trademark NOVAMYL® has been noted in this application at paragraphs [0002], [0004], [0019], [0040], [0068], [0071], [0076], [0077], [0078], [0079], [0080], [0081], [0082], [0083], [0084], and [0087]. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Objection

4. Claim 6 is objected to for the following reason: There appears to be an inconsistency with the punctuation marks. For example, claim 6a) ends with a semicolon (;). Claim 6b) and 6c) end with a comma (,). To be consistent throughout the claim, the punctuation marks should be corrected.

Rejection

35 U.S.C. 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 10 recites, "The polypeptide of claim 6, which comprises an amino acid residue which is present at the corresponding position of SEQ ID NO: 17 or deletion of an amino acid residue in SEQ ID NO: 6 which is not present at the corresponding position in the amino acid sequence shown in SEQ ID NO: 17." The claim does not particularly point out and distinctly define the metes and bounds of the subject matter. It

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is unclear what amino acid residue is present at what "corresponding position of SEQ ID NO: 17" and is meant by "deletion of an amino acid residue in SEQ ID NO: 6" in relation to "corresponding position in the amino acid sequence shown in SEQ ID NO: 17." For example, SEQ ID NO: 17 has 686 amino acids; SEQ ID NO: 6 has 683 amino acids. SEQ ID NO: 17 has the starting sequence SSSASVKGDVIYGIIDRFY...and SEQ ID NO: 6 has the starting sequence APDTSVSNVNYSTDVIYQI...Comparing the first twenty amino acids, the residues that are present in SEQ ID NO: 17, but not in SEQ ID NO: 6 are SSSA, KGD, I, GIIDRFY. These are not contiguous. Therefore, it is unclear what corresponding amino acid the Applicant is referring to.

8. Claim 12 recites, "The polypeptide of claim 6 which compared to SEQ ID NO: 6 has a substitution corresponding to V16A, K47K...G153V/G..." It is unclear how a substitution of Lysine at position 47 can be another lysine. It is unclear how a substitution of glycine at position 153 can be another glycine.

9. Claim 12 recites the limitation "K47K," "G153V/G," "N194S," and "R353H" in the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 12 is dependent from claim 6. Claim 6a) recites, "has an amino acid sequence having at least 70% identity to SEQ ID NO: 6". Claim 6b) recites, "...comprises at least one additional amino acid in a region corresponding to amino acids 194-198". Claim 6c) recites, "...has a different amino acid or an insertion or deletion at a position corresponding to amino acid 16, 47, 85-95, 117, 139, 145, 146, 152, 153, 168, 169, 174, 184, 191, 260-269, 285, 288, 298, 314, 335, 413, 556, 602 or 677". According to claim 6b) there is at least one additional amino acid in a region corresponding to amino acids 194-198. According

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to claim 6c) there is a different amino acid or an insertion or deletion at one of the above positions. In regards to "N194S", claim 6b) does not indicate that there is any substitution; claim 6c) does not recite amino acid position 194. Therefore, a substitution at position 194 lacks antecedent basis. In regards to "K47K" and "G153V/G", claim 6c) recites that there is a different amino acid (substitution) at one of the positions. Since K to K and G to G do not imply substitutions, these lack antecedent basis. In regards to "R353H", this position is not recited in claim 6. Therefore, R353H lacks antecedent basis. Thus, claim 12 lacks antecedent basis.

35 U.S.C. 112, first paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 6, 8-10, 12 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is

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claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when

accompanied by a method of obtaining the claimed sequence.” MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a polypeptide which (a) has an amino acid sequence having at least 70% identity to SEQ ID NO: 6; (b) comprises at least one additional amino acid in a region corresponding to amino acids 194-198 of SEQ ID NO: 6; (c) has a different amino acid or an insertion or deletion at a position corresponding to amino acid 16, 47, 85-95, 117, 139, 145, 146, 152, 153, 168, 169, 174, 184, 191, 260-269, 285, 288, 298, 314, 335, 413, 556, 602 or 677 of SEQ ID NO: 6; and (d) has the ability to form linear oligosaccharides as an initial product when acting on starch. The generic statements at least 70% identity to SEQ ID NO: 6, has at least one additional amino acid in a region corresponding to amino acids 194-198 of SEQ ID NO: 6, has a different amino acid or an insertion or deletion at a position corresponding to amino acid 16, 47, 85-95, 117, 139, 145, 146, 152, 153, 168, 169, 174, 184, 191, 260-269, 285, 288, 298, 314, 335, 413, 556, 602 or 677, and has the ability to form linear oligosaccharides do not provide ample written description for the compounds since the

claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 6 is broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide or amide bonds, and make up the class of polypeptides. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives or variants or homologs. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules that can form peptide bonds, amino acid mimetics, or peptidomimetics, and other synthetic peptide or peptide-like molecule that can function as polypeptides.

The specification discloses that "a selected CGTase residue may be deleted or may be substituted with a different residue. The substitution may be made with the same amino acid residue as found at a corresponding position in an alignment with the maltogenic alpha-amylase sequence or with a residue of the same type. The type indicates a positively charged, negatively charged, hydrophilic or hydrophobic residue (see paragraph [0048] of instant specification US 2007/0148287). The specification discloses that the maltogenic alpha-amylase is represented by SEQ ID NO: 17 (see paragraph [0040]). The specification discloses that one or more amino acid residues may be inserted at a position adjacent to the selected CGTase residue on the amino or carboxyl side...may be made at a position in the CGTase sequence where the maltogenic amylase contains additional residues, and the insertion may consist of an equal number of residues, or the insertion may have one or two fewer or more residues (see paragraph [0054]). The specification discloses that the insertion at residues 193-200 may particularly consist of 1-7 residues, e.g., 1, 2, 3, 4, 5, 6 or 7 residues, and may particularly consist of DPAGF, e.g. between residues 196 and 197 of SEQ ID NO: 5 (see paragraph [0056]). The specification discloses that "the substitution according to the invention may improve the thermostability of the CGTase variants" (see paragraph [0065])...optionally, the amino acid sequence may be further modified to improve the properties of the variant, particularly to improve its thermostability (see paragraph [0066]). Furthermore, the specification discloses that CGTase may be modified by substitution, insertion or deletion of an amino acid at a position 85-95, 152, 184, 260-

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269, 285, 288, 314 of the amino acid sequence of SEQ ID NO: 5 or 6 (see paragraph [0068]).

The working Example 2 describes starch hydrolysis of CGTase variants.

Example 2 discloses that nine variants (7 variants of SEQ ID NO: 6 and 2 variants of SEQ ID NO: 12) prepared in Example 1 were tested to determine the initial product profile in starch hydrolysis. No data was provided. The working Example 3 describes baking tests with CGTase variants (7 variant of SEQ ID NO: 6 and 3 variants of SEQ ID NO: 12). The specification indicates that each of the variants was ranked better than a control without enzyme...the bread made with GCTase was gummy and unacceptable (see paragraph [0094]). No data was provided.

The specification does not describe any other polypeptide having at least 70% sequence homology to SEQ ID NO: 6, having at least one additional amino acid at position 194-198 of SEQ ID NO: 6, has a different amino acid or an insertion or deletion at different positions, such as synthetic small molecules that functions as amino acid or polypeptide, amino acid mimetics, peptidomimetics or non-natural amino acids that can form peptide bonds. Description of polypeptide having DPAGF insertion at region corresponding to amino acids 194-198 of SEQ ID NO: 6 or having a different amino acid or an insertion or deletion at a position corresponding to those recited in the claims is not sufficient to encompass numerous other polypeptides that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, SEQ ID NO: 6 has 683 amino acids. A polypeptide having at least 70% sequence homology has 204

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different amino acids ($683 \times 0.70 = 478.1$). There are 20 naturally occurring amino acids. This implies just for 20 naturally occurring amino acids, there are $20^{46} = 1.56 \times 10^{46}$ different possibilities. When non-natural amino acids (such as D-amino acids, protected amino acids, β -amino acids, γ -amino acids, ϵ -amino acids) are factored into the equation, there are vast numbers of possibilities. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

12. Claims 6, 8-10, 12, 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising additional DPAGF sequence in the region corresponding to 194-198, does not reasonably provide enablement for all additional amino acids in a region corresponding to amino acids 194-198, and all polypeptide having at least 70% identity to SEQ ID NO: 6 comprising at

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least one additional amino acid, different amino acids, insertions or deletions to SEQ ID NO: 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (5) the breadth of the claims:

The claims are drawn to (a) a polypeptide comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 6; (b) comprises at least one additional amino acid in a region corresponding to amino acids 194-198 of SEQ ID NO: 6; (c) has a different amino acid or an insertion or deletion at a position corresponding to amino acid 16, 47, 85-95, 117, 139, 145, 146, 152, 153, 168, 169, 174, 184, 191, 260-269,

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285, 288, 298, 314, 335, 413, 556, 602 or 677, and (d) has the ability to form linear oligosaccharide as an initial product when acting on starch.

(2) The state of the prior art and (4) the predictability or unpredictability of the art::

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (Peptide Hormones, JA Parsons, Ed., 1976, 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study" (see p. 6). Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Additionally, Schinzel et al (FEBS, 1991, 286(1, 2): 125-128) teach that the substitution of Lys⁵³⁹ by an arginine caused a 600 fold reduction, substitution of Arg⁵³⁴ by a glutamine caused an even larger 7000-fold reduction of the catalytic rate while substrate binding remained essentially unaffected. The reference teaches that Arg⁵³⁴ to Gln exchange reduces the catalytic rate near to inactivity and even the conservative Lys⁵³⁴ to Arg exchange caused marked decrease of activity (see abstract).

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26) β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6) β (see p. 236), which

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results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Additionally, the art recognizes that “The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study”. Additionally, SIGMA states that with regards to design of peptide sequences that, “Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine” (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Therefore, any modification on the polypeptide might have an affect on the polypeptide, thus vast numbers of experimentation would be required to see if the polypeptide modified with the oxime-containing non-natural amino acid would have the same affect on certain diseases as the wild-type polypeptide. As with all peptides, activity is based on the structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the peptide to be active. The state of the art for prediction of the native conformation of the protein is, at best, a vague science. For example, in peptide chemistry, Ngo et al teach that for protein and peptides, a “‘Direct’ approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task” (see p. 493). Accordingly, it is not known if an efficient algorithm for

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predicting the structure exists for a protein or peptide from its amino acid alone (see p. 492). Thus, activity of a given peptide cannot be based on its structure alone. Similarly, the Rudinger article (see the conclusion in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from the case to case by painstaking experimental study." Finally, in an article published in Science, the author concluded that "one of the 'grand challenges' of high-performance computing-predicting the structure of proteins-acquires much of the flavor of the Holy Grail-quest of the legendary knights of King Arthur. It is extremely desirable to possess but extremely elusive to obtain" (see p. 643 in Berendsen). Berendsen et al states "at the present level of sophistication, [homology modeling] are effective for only 25% of the proteins for which the amino acid sequence is known" (see p. 642). It is known that proteins fold into their native conformation spontaneously and within seconds. The underlying principle of folding is known in the art yet the art lacks the ability to mimic native folding process (see p. 642 in Berendsen). "[E]xisting computers cannot sample enough configurations in a reasonable time to come up with the thermodynamically stable native structure;...we are not too sure that the available force field descriptions, which we need to compute the energy of a each configuration, are accurate enough to come up with reliable free energy of a conformation" (see p. 642 in Berendsen). Berendsen et al discloses the principle of the "Levinthal's paradox" which states that if one was to assume that "three possible states for every flexible dihedral angle in the backbone of a 100 protein residue, the number of possible backbone configuration is 3^{200} . Even an

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incredibly fast computational or physical sample in 10^{-15} s would mean that complete sample would take 10^{80} s, which exceeds that age of the universe by more than 60 orders of magnitude.” Other tools such as lattice models provide insight into principle of folding, but to provide no solutions to the real folding problems (see p. 643 in Berendsen). The art has recognized that even single point mutations can cause diverse effects on peptide activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle cell anemia can be traced to a single point mutation at position six in the beta globulin protein. The instant application claims are open to oxime modification at any position of any therapeutic polypeptides. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type therapeutic polypeptides.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any peptide having at least 70% sequence identity to SEQ ID NO: 6 that has the same activity as the claimed protein,

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one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification discloses that “a selected CGTase residue may be deleted or may be substituted with a different residue. The substitution may be made with the same amino acid residue as found at a corresponding position in an alignment with the maltogenic alpha-amylase sequence or with a residue of the same type. The type indicates a positively charged, negatively charged, hydrophilic or hydrophobic residue (see paragraph [0048] of instant specification US 2007/0148287). The specification discloses that the maltogenic alpha-amylase is represented by SEQ ID NO: 17 (see paragraph [0040]). The specification discloses that one or more amino acid residues may be inserted at a position adjacent to the selected CGTase residue on the amino or carboxyl side...may be made at a position in the CGTase sequence where the maltogenic amylase contains additional residues, and the insertion may consist of an equal number of residues, or the insertion may have one or two fewer or more residues (see paragraph [0054]). The specification discloses that the insertion at residues 193-

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200 may particularly consist of 1-7 residues, e.g., 1, 2, 3, 4, 5, 6 or 7 residues, and may particularly consist of DPAGF, e.g. between residues 196 and 197 of SEQ ID NO: 5 (see paragraph [0056]). The specification discloses that "the substitution according to the invention may improve the thermostability of the CGTase variants" (see paragraph [0065])...optionally, the amino acid sequence may be further modified to improve the properties of the variant, particularly to improve its thermostability (see paragraph [0066]). Furthermore, the specification discloses that CGTase may be modified by substitution, insertion or deletion of an amino acid at a position 85-95, 152, 184, 260-269, 285, 288, 314 of the amino acid sequence of SEQ ID NO: 5 or 6 (see paragraph [0068]).

The working Example 2 describes starch hydrolysis of CGTase variants. Example 2 discloses that nine variants (7 variants of SEQ ID NO: 6 and 2 variants of SEQ ID NO: 12) prepared in Example 1 were tested to determine the initial product profile in starch hydrolysis. No data was provided. The working Example 3 describes baking tests with CGTase variants (7 variant of SEQ ID NO: 6 and 3 variants of SEQ ID NO: 12). The specification indicates that each of the variants was ranked better than a control without enzyme...the bread made with GCTase was gummy and unacceptable (see paragraph [0094]). No data was provided.

The specification does not describe any other polypeptide having at least 70% sequence homology to SEQ ID NO: 6, having at least one additional amino acid at position 194-198 of SEQ ID NO: 6, has a different amino acid or an insertion or deletion at different positions, such as synthetic small molecules that functions as amino acid or

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polypeptide, amino acid mimetics, peptidomimetics or non-natural amino acids that can form peptide bonds. Description of polypeptide having DPAGF insertion at region corresponding to amino acids 194-198 of SEQ ID NO: 6 or having a different amino acid or an insertion or deletion at a position corresponding to those recited in the claims is not sufficient to encompass numerous other polypeptides that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, SEQ ID NO: 6 has 683 amino acids. A polypeptide having at least 70% sequence homology has 204 different amino acids ($683 \times 0.70 = 478.1$). There are 20 naturally occurring amino acids. This implies just for 20 naturally occurring amino acids, there are $204^{20} = 1.56 \times 10^{46}$ different possibilities. When non-natural amino acids (such as D-amino acids, protected amino acids, β -amino acids, γ -amino acids, ϵ -amino acids) are factored into the equation, there are vast numbers of possibilities. However, the specification does not provide for the myriad of peptides embraced by the broad generic or for the myriad of polypeptides having at least 70% sequence identity, having insertions, substitutions or deletions to SEQ ID NO: 6.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the reference above and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make a polypeptide having at least 70% sequence identity to SEQ ID NO: 6, having at least one

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additional amino acid in a region corresponding to amino acids 194-198 of SEQ ID NO: 6 and having a different amino acid or an insertion or deletion at a position corresponding to amino acid as described above that would have the same function (has the ability to form linear oligosaccharides as an initial product when acting on starch) as the claimed polypeptide. Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any polypeptide having at least 70% sequence identity to SEQ ID NO: 6, having at least one additional amino acid in a region corresponding to amino acids 194-198 of SEQ ID NO: 6 and having a different amino acid or an insertion or deletion at a position corresponding to amino acid as described above that has the same activity as the claimed protein/ polypeptide, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

35 U.S.C. 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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14. Claims 6, 8-10, 12, 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Cherry et al (WO 99/43793, filed with IDS).

15. Cherry et al teach a CGTase variants having at least 70% sequence identity to instant SEQ ID NO: 6 (see SEQ ID NO: 1, p. 4, lines 1-2, and Figure 4). The reference teaches that SEQ ID NO: 1 has at least 70% sequence identity to instant SEQ ID NO: 6, and has a lysine at position 47. The reference teaches that maltogenic alpha-amylase (glucan 1,4-a-maltohydrolase, E.C. 3.2.1.133) and is commercially available under the trade name NOVAMYL® (see p. 1, bottom of the page). The reference teaches that the CGTase variant may particularly comprise an insertion into a position corresponding to the region D190-F194 of NOVAMYL (see p. 4, line 25) (amino acid sequence shown in SEQ ID NO: 1). The insertion may comprise 3-7 amino acids, particularly 4-6, e.g. amino acids (DPAGF found in NOVAMYL or an analogue thereof) (see p. 4, lines 22-30 and see Figure 4), meeting the limitation of claims 6, 8-10 and 15-16. These positions correspond to positions 196 and 197 of instant SEQ ID NO: 6. The reference teaches that there is a lysine residue at position 47, meeting the limitation of claims 6 and 12. Since the reference teaches a peptide having at least 70% sequence identity to instant SEQ ID NO: 6, this polypeptide would inherently have all of the characteristics and functionalities of instantly claimed polypeptide. Therefore, the reference anticipates instant claims 6, 8-10, 12 and 15-17.

Conclusion

16. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982.

The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654